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## (54) Novel 8-substituted purines as selective adenosine receptor agents.

(57) The present invention relates to certain novel 8-substituted purines as selective $A_1$-adenosine receptor antagonists which are useful in the treatment of patients suffering from Alzheimer's disease, congestive heart failure or pulmonary bronchoconstriction.

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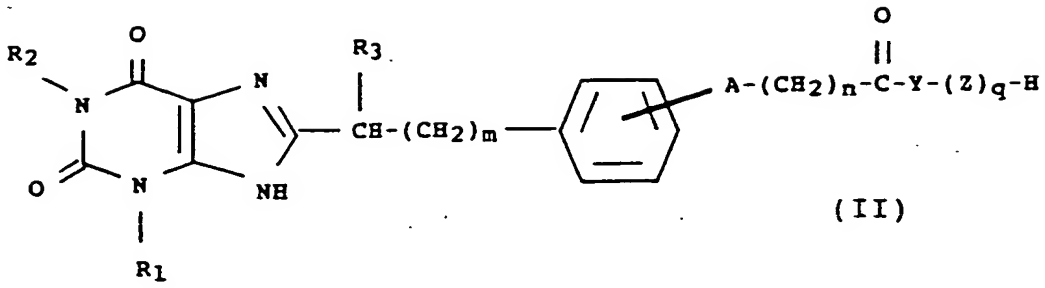
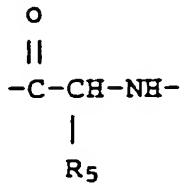


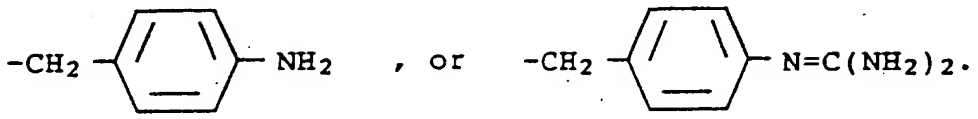
(II)

wherein

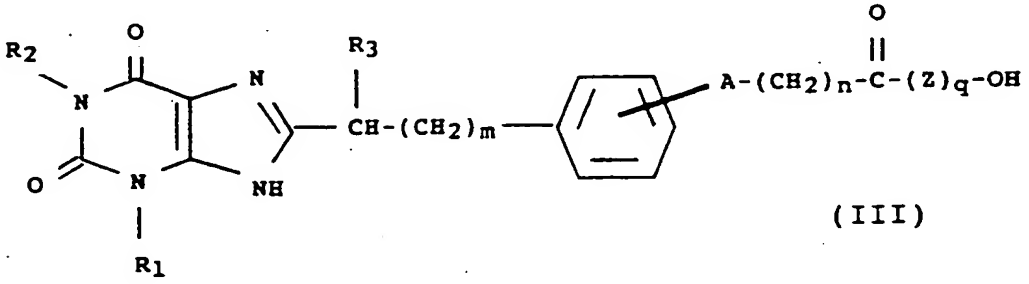
$R_1$, $R_2$ and $R_3$ are each independently a $C_1$-$C_4$ alkyl,
m is an integer 0, 1 or 2,
A is O, S, or NH,
n is an integer 1, 2 or 3,
Y is $-NH(CH_2)_pNH-$,
p is an integer 2, 3 or 4,
Z is a radical of the formula



q is an integer 0, 1, 2 or 3, and
$R_5$ is a radical selected each time taken from the group consisting of H, $CH_3$, $-CH(CH_3)_2$, $-CH(CH_3)-CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2N=C(NH_2)_2$, $-CH_2CH_2CH_2CH_2N=C(NH_2)_2$,



The present invention also relates to novel [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]-phenylhetero alkanamide peptides of formula (III)

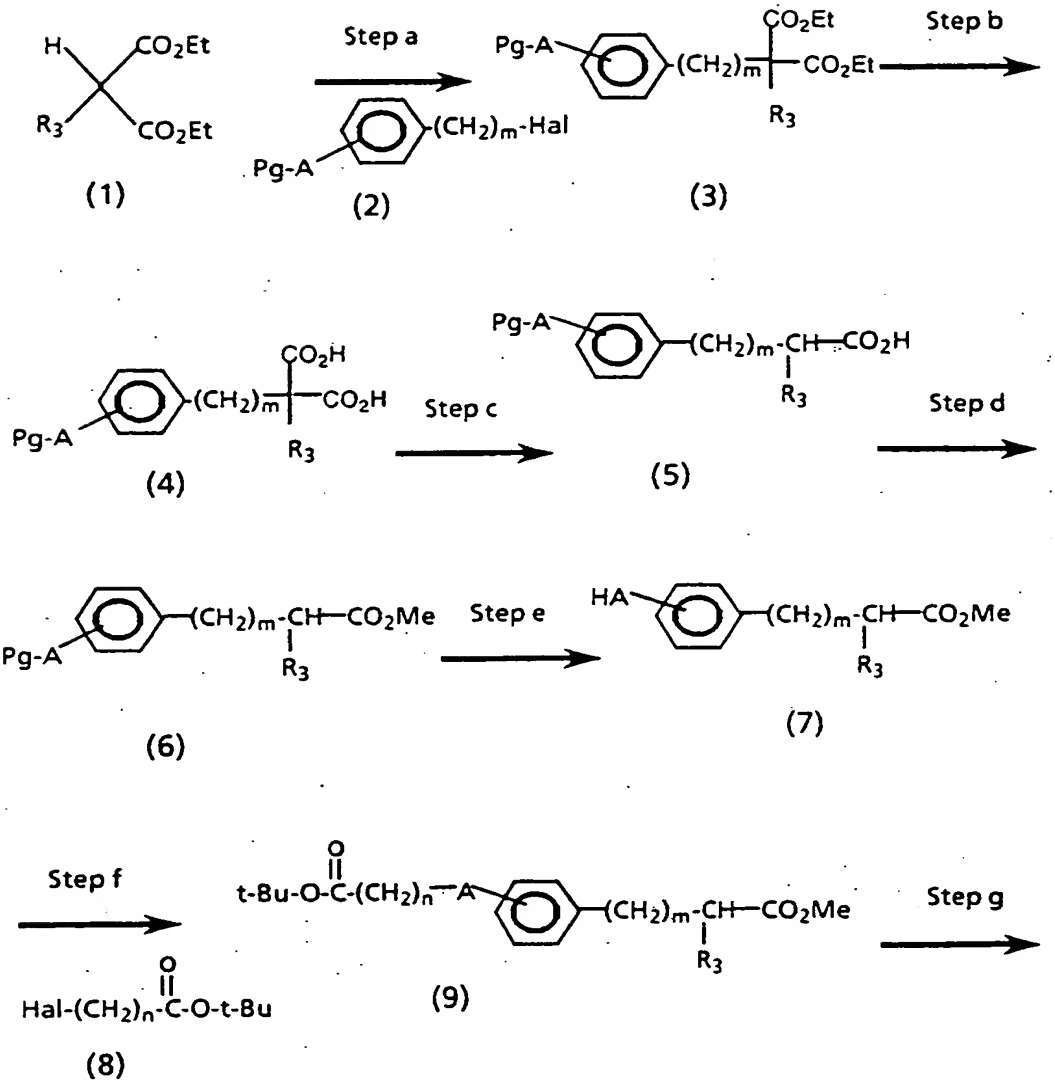


(III)

wherein

$R_1$, $R_2$ and $R_3$ are each independently a $C_1$-$C_4$ alkyl,
m is an integer 0, 1 or 2,
A is O, S, or NH,

Scheme A


H
CO2Et
R3
CO2Et
(1)
Step a
Pg-A
(CH2)m-Hal
(2)
CO2Et
Pg-A
(CH2)m
CO2Et
R3
(3)
Step b
CO2H
Pg-A
(CH2)m
CO2H
R3
(4)
Step c
Pg-A
(CH2)m-CH—CO2H
R3
(5)
Step d
Pg-A
(CH2)m-CH—CO2Me
R3
(6)
Step e
HA
(CH2)m-CH—CO2Me
R3
(7)
Step f
O
Hal-(CH2)n-C-O-t-Bu
(8)
O
t-Bu-O-C-(CH2)n—A
(CH2)m-CH—CO2Me
R3
(9)
Step g

Due to the conditions of the alkylation reaction, it is necessary that the hetero substituted-(haloalkyl)-benzene of structure (2) be protected. The selection and utilization of suitable protecting groups are well known to one of ordinary skill in the art and are described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981).

In step b, the appropriate diethyl dialkylmalonate of structure (3) is hydrolyzed under basic conditions to the corresponding dialkyl malonic acid of structure (4). For example, the diethyl dialkylmalonate of structure (3) is contacted with a molar excess of potassium hydroxide. The reactants are typically contacted in a protic solvent system such as ethanol/water. The reactants are typically stirred together for a period of time ranging from about 1 to 6 hours and at a temperature range of room temperature to reflux. The reaction mixture is then acidified with an appropriate acid, such as hydrochloric acid. The dialkylmalonic acid as described by structure (4) can be recovered from the reaction zone by techniques such as filtration.

In step c, the dialkylmalonic acid of structure (4) is decarboxylated to give the corresponding 2-alkyl-alkanoic acid of structure (5). Typically, the dialkylmalonic acid of structure (4) is contacted with a catalytic amount of copper(I) oxide in a suitable organic solvent such as acetonitrile. The reactants are typically stirred together for a period of time ranging from 2 to 24 hours and at a temperature range from room temperature to reflux. The 2-alkyl-alkanoic acid of structure (5) can be recovered from the reaction zone by extractive methods as is known in the art.

In step d, the 2-alkyl-alkanoic acid of structure (5) is esterified under acidic conditions to give the corresponding methyl 2-alkyl-alkanoate of structure (6). For example, the 2-alkyl-alkanoic acid of structure (5) is contacted with a molar excess of methanol and a catalytic amount of sulfuric acid. The reactants are typically stirred together for a period of time ranging from 5-24 hours and at a temperature range of from room temperature to reflux. The methyl 2-alkyl-alkanoate of structure (6) can be recovered from the reaction zone by extractive methods as is known in the art.

In step e, the hetero protecting group functionality of the methyl 2-alkyl-alkanoate of structure (6) is removed to give the unprotected methyl-2-alkyl-alkanoate of structure (7). The removal of protecting groups is well known to one of ordinary skill in the art and is described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981).

In step f, the hetero functionality of the unprotected methyl-2-alkyl-alkanoate of structure (7) is alkylated with the appropriate t-butyl haloalkanoate of structure (8) under basic conditions to give the 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid, methyl ester of structure (9). For example, the unprotected methyl-2-alkyl-alkanoate of structure (7) is contacted with a molar excess of the appropriate t-butyl haloalkanoate of structure (8), a molar excess of a suitable base, such as potassium carbonate, and a catalytic amount of potassium iodide. The reactants are typically contacted in a organic solvent such as acetone. The reactants are typically stirred together for a period of time ranging from 24 to 200 hours and at a temperature range of from room temperature to reflux. The 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid, methyl ester of structure (9) is recovered from the reaction zone by extractive methods and purified by silica gel chromatography as is known in the art.

In step g, the methyl ester functionality of the appropriate 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid, methyl ester of structure (9) can be hydrolyzed to give the corresponding 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid of structure (10).

One method for carrying out the hydrolysis reaction of step g is to contact the 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid, methyl ester of structure (9) with an equimolar amount of sodium cyanide. The reactants are typically contacted in a organic solvent such as anhydrous hexamethylphosphoramide. The reactants are typically stirred together for a period of time ranging from 24 to 64 hours and at a temperature range of from room temperature to 70°C. The 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid of structure (10) is recovered from the reaction zone by extractive methods and purified by silica gel chromatography as is known in the art.

Another method for carrying out the hydrolysis reaction of step g is to contact the 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid, methyl ester of structure (9) with an molar excess of lithium propyl mercaptide. The reactants are typically contacted in an organic solvent such as anhydrous hexamethylphosphoramide. The reactants are typically stirred together for a period of time ranging from 2 to 24 hours and at a temperature range of from room temperature to 70°C. The 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid of structure (10) is recovered from the reaction zone by extractive methods and purified by silica gel chromatography as is known in the art.

In order to prepare compounds of formula (I) which are enantomerically pure, it is necessary to carry out a selective hydrolysis reaction in step g. For example, in order to prepare the (+)-enantiomer of the appropriate compound of formula (I), it is necessary to prepare the (+)-enantiomer of the appropriate 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid of structure (10). Analogously, in order to

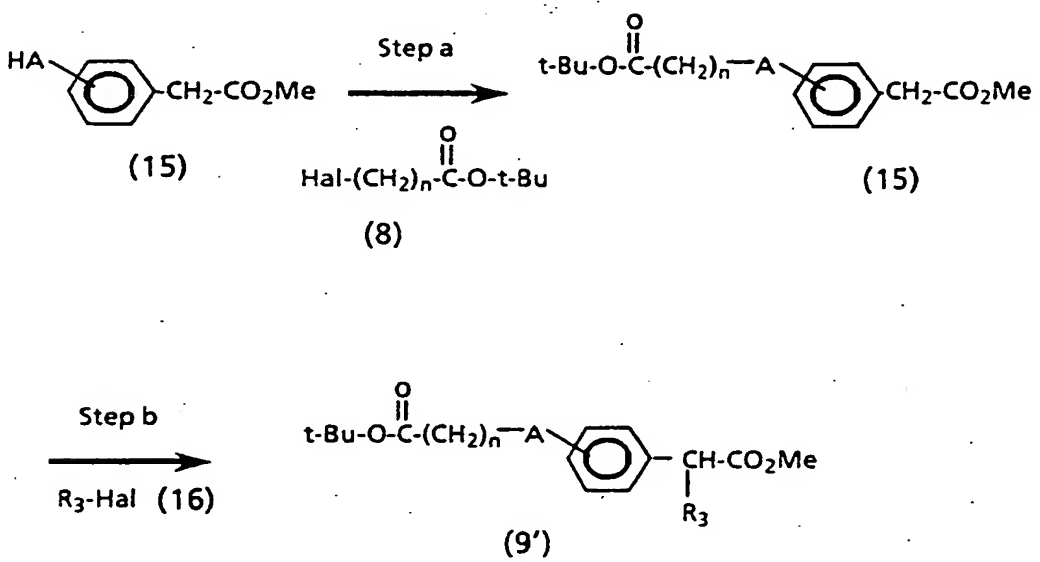
The ethyl imino ether of the [[[[6-amino-1,3-dialkyl-1,2,3,4 -tetrahydro-2,4-dioxo-5-pyrimidinyl]amino]-oxoalkyl]phenyl]hetero alkanoic acid, t-butyl ester of structure (12) is then cyclized to the ethyl ester of the [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]phenylhetero alkanoic acid of structure (13) by heating. Typically, the ethyl imino ether of the [[[[6-amino-1,3-dialkyl-1,2,3,4-tetrahydro-2,4-dioxo-5-pyrimidinyl]amino]oxoalkyl]phenyl]hetero alkanoic acid, t-butyl ester of structure (12) is contacted with an organic solvent, such as benzene and stirred at 80°C for a period of time ranging from 5-48 hours. The ethyl ester of the [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]phenylhetero alkanoic acid of structure (13) is recovered from the reaction zone by extractive methods as is known in the art and purified by silica gel chromatography.

The ethyl ester of the [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]phenylhetero alkanoic acid of structure (13) is then hydrolyzed to the [[2,3,6,9-tetrahydro -1,3-dialkyl-2,6-dioxo-1H-purin-8-yl] alkyl]phenylhetero alkanoic acid of structure (13). The ethyl ester of the [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]phenylhetero alkanoic acid of structure (13) is contacted with an equimolar amount of a base, such as potassium hydroxide in a protic solvent system, such as ethanol/water. Typically the reactants are stirred together for a period of time ranging from 1-24 hours and at a temperature range of from -10°C to room temperature. The [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]-phenylhetero alkanoic acid of structure (13) is recovered from the reaction zone by first acidification and extractive methods as is known in the art. It can be purified by silica gel chromatography.

In optional step j, the [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl)phenylhetero alkanoic acid of structure (13) may be esterified to give the [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]-alkyl]phenylhetero alkanoic acid, alkyl ester of structure (14). Typically, the [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]phenylhetero alkanoic acid of structure (13) is contacted with a molar excess of an appropriate alcohol and a catalytic amount of an acid, such as concentrated sulfuric acid. The reactants are typically stirred together for a period of time ranging from 5-24 hours and at a temperature range of from room temperature to reflux. The [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]-phenylhetero alkanoic acid, alkyl ester of structure (14) is recovered from the reaction zone by evaporation of the solvent and purification by silica gel chromatography.

An alternative synthetic procedure for the preparation of the 1,1-dimethylethoxy-oxoalkylhetero-alpha-alkyl-benzenealkanoic acid, methyl ester of structure (9'), wherein m = 0, for use in the preparation of compounds of formula (I) wherein m = 0 is set forth in Scheme B. In Scheme B, all substituents, unless otherwise indicated, are as previously defined.

## Scheme B



methyl-(4-benzyloxy)benzylmalonate (74.5g, 0.2mol) and heat at reflux for 3 hours. Cool to 0°C and carefully treat with concentrated hydrochloric acid (140mL) and water (300mL). Filter the solid and dry to give the title compound (65g).

Scheme A, Step c: 2-Methyl-3-(4-benzyloxy)phenyl propionic acid

Suspend methyl-(4-benzyloxy)benzylmalonic acid (65g, 0.2mol) in acetonitrile (800mL) and treat with copper(I) oxide (1.5g, 0.01mol). Heat at reflux for 7 hours. Cool, filter and evaporate the solvent *in vacuo*. Take the residue up in ethyl ether (1L) and wash with 10% hydrochloric acid (2X500mL), water (500mL) and brine (500mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound (53.3g, 98%).

Scheme A, Step d: Methyl [2-methyl-3-(4-benzyloxy)phenyl]propionate

Dissolve 2-methyl-3-(4-benzyloxy)phenyl propionic acid (53.3g, 0.2mol) in methanol (500mL) and treat with concentrated sulfuric acid (0.5mL). Heat to 60°C for 16 hours, cool and reduce the solvent by 50% *in vacuo*. Dilute with ethyl ether (500mL), wash with saturated sodium hydrogen carbonate, then brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound (54.2g, 95%)

Scheme A, Step e: Methyl [2-methyl-3-(4-hydroxy)phenyl]propionate

Dissolve methyl [2-methyl-3-(4-benzyloxy)phenyl]propionate (13.3g, 46.8mmol) in methanol (300mL) and treat with 5% palladium/carbon (1g). Place under an atmosphere of hydrogen and stir vigorously for 4 hours. Filter through filter aid and evaporate the solvent *in vacuo* to give the title compound (9.1g, 100%).

Scheme A, Step f: 4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid, methyl ester

Dissolve methyl [2-methyl-3-(4-hydroxy)phenyl]propionate (13.7g, 70.5mmol) in acetone (500mL) and treat with potassium carbonate (10.7g, 77.6mmol), potassium iodide (1.17g, 7.05mmol) and t-butyl bromoacetate (15.1g, 77.6mmol). Reflux for 168 hours, cool, filter and evaporate the solvent in vacuo. Purify by flash chromatography (5⇒10⇒15% isopropranol/hexane) to give the title compound (19.84g).

Scheme A, Step g: 4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid

Dissolve 4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid, methyl ester (10g, 32.4mmol) in anhydrous hexamethylphosphoramide (160mL) and treat with sodium cyanide (1.59g, 32.4mmol). Heat at 70°C for 48 hours, cool and dilute with saturated ammonium chloride (300mL). Extract with ethyl ether (400mL), wash with water (2X300mL), then brine (300mL) and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by flash chromatography (5⇒10% methanol/chloroform) to give the title compound (1.09g).

Scheme A, Step h: 2-[[4-[3-[(6-Amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]oxy]-acetic acid, 1,1-dimethylethyl ester

Dissolve 4-[[2(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid (1.07g, 3.64mmol) in tetrahydrofuran (15mL) and treat with N-methylmorpholine (0.4mL, 3.64mmol). Cool to -20°C and treat with isobutyl chloroformate (0.47mL, 3.64mmol). Stir for 30 minutes and add a solution of 1,3-dipropyl-5,6-diaminouracil (0.82g, 3.64mmol) in dimethylformamide (5mL). Stir for 3 hours at - 20°C, warm to room temperature and dilute with ethyl ether (200mL). Separate the organic phase, wash with water (200mL) and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by flash chromatography (5⇒10% methanol/chloroform then 5⇒10⇒20% isopropanol/hexane) to yield the title compound (1.66g).

Scheme A, Step i: 2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]aceticacid

Dissolve 2-[[4-[3-[(6-amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]oxy]-acetic acid, 1,1-dimethylethyl ester (1.6g, 3.18mmol) in a mixture of ethanol (30mL) and 15% potassium hydroxide (30mL). Heat at 55°C and stir for 5 hours. Cool, acidify and dilute with water (200mL). Filter to give 0.69g crude product. Recrystallize (5% isopropanol/hexane) to give the title

Suspend methyl-(4-methylthio)benzylmalonic acid (508mg, 0.2mol) in acetonitrile (800mL) and treat with copper(I) oxide (1.5g, 0.01mol). Heat at reflux for 7 hours. Cool, filter and evaporate the solvent *in vacuo*. Take the residue up in ethyl ether (1L) and wash with 10% hydrochloric acid (2X500mL), water (500mL) and brine (500mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound.

Scheme A, Step d: Methyl [2-methyl-3-(4-methylthio)phenyl]propionate

Dissolve 2-methyl-3-(4-methylthio)phenyl propionic acid (420mg, 0.2mol) in methanol (500mL) and treat with concentrated sulfuric acid (0.5mL). Heat to 60°C for 16 hours, cool and reduce the solvent by 50% *in vacuo*. Dilute with ethyl ether (500mL), wash with saturated sodium hydrogen carbonate, then brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound.

Scheme A, Step e: Methyl [2-methyl-3-(4-thio)phenyl]propionate

Dissolve methyl [2-methyl-3-(4-methylthio)phenyl]propionate (1.12g, 5mmol) in chloroform (20mL) and treat with metachloroperbenzoic acid (863mg, 5mmol). Add calcium hydroxide (556mg, 7.5mmol) and stir for 15 minutes. Filter and evaporate the solvent *in vacuo*. Dissolve the residue in trifluoroacetic anhydride (10mL) and heat at reflux for 30 minutes. Evaporate the volatiles *in vacuo* and dissolve the residue in a mixture of methanol-triethylamine (1:1, 100mL) and evaporate the solvent *in vacuo*. Dissolve the residue in chloroform, wash with saturated ammonium chloride and dry ($MgSO_4$). Evaporate the solvent *in vacuo* to give the title compound.

Scheme A, Step f: 4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]thio]-alpha-methyl-benzenepropanoic acid, methyl ester

Dissolve methyl [2-methyl-3-(4-thio)phenyl)propionate (14.8g, 70.5mmol) in acetone (500mL) and treat with potassium carbonate (10.7g, 77.6mmol), potassium iodide (1.17g, 7.05mmol) and t-butyl bromoacetate (15.1g, 77.6mmol). Reflux for several hours, cool, filter and evaporate the solvent *in vacuo*. Purify by flash chromatography to give the title compound.

Scheme A, Step g: 4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]thio]-alpha-methyl-benzenepropanoic acid

Dissolve 4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]thio]-alpha-methyl-benzenepropanoic acid, methyl ester (10.5g, 32.4mmol) in anhydrous hexamethylphos-phoramide (160mL) and treat with sodium cyanide (1.59g, 32.4mmol). Heat at 70°C for 48 hours, cool and dilute with saturated ammonium chloride (300mL). Extract with ethyl ether (400mL), wash with water (2X300mL), then brine (300mL) and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by flash chromatography to give the title compound.

Scheme A, Step h: 2-[[4-[3-[(6-Amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]thio]-acetic acid, 1,1-dimethylethyl ester

Dissolve 4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]thio]-alpha-methyl-benzenepropanoic acid (1.13g, 3.64mmol) in tetrahydrofuran (15mL) and treat with N-methylmorpholine (0.4mL, 3.64mmol). Cool to -20°C and treat with isobutyl chloroformate (0.47mL, 3.64mmol). Stir for 30 minutes and add a solution of 1,3-dipropyl-5,6-diaminouracil (0.82g, 3.64mmol) in dimethylformamide (5mL). Stir for 3 hours at - 20°C, warm to room temperature and dilute with ethyl ether (200mL). Separate the organic phase, wash with water (200mL) and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by flash chromatography to yield the title compound.

Scheme A, Step i: 2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylthio]acetic acid

Dissolve 2-[[4-[3-[(6-amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]thio]-acetic acid, 1,1-dimethylethyl ester (1.65g, 3.18mmol) in a mixture of ethanol (30mL) and 15% potassium hydroxide (30mL). Heat at 55°C and stir for several hours. Cool, acidify and dilute with water (200mL). Filter the precipitate and dry to give the title compound.

Example 4

carefully treat with concentrated hydrochloric acid (140mL) and water (300mL). Filter the solid and dry to give the title compound.

Scheme A, Step c: 2-Methyl-3-(4-benzylamino)phenyl propionic acid

Suspend methyl (4-benzylamino)benzylmalonic acid (62.6g, 0.2mol) in acetonitrile (800mL) and treat with copper(I) oxide (1.5g, 0.01mol). Heat at reflux for 7 hours. Cool, filter and evaporate the solvent *in vacuo*. Take the residue up in ethyl ether (1L) and wash with 10% hydrochloric acid (2X500mL), water (500mL) and brine (500mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound.

Scheme A, Step d: Methyl [2-methyl-3-(4-benzylamino)phenyl]propionate

Dissolve 2-methyl-3-(4-benzylamino)phenyl propionic acid (53.6g, 0.2mol) in methanol (500mL) and treat with concentrated sulfuric acid (0.5mL). Heat to 60°C for 16 hours, cool and reduce the solvent by 50% *in vacuo*. Dilute with ethyl ether (500mL), wash with saturated sodium hydrogen carbonate, then brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound.

Scheme A, Step e: Methyl [2-methyl-3-(4-amino)phenyl]propionate

Dissolve methyl [2-methyl-3-(4-benzylamino)phenyl]propionate (200mg, 0.71mmol) in formic acid (10mL of a 4.4% solution in methanol) and add to a suspension to freshly prepared palladium black catalyst (200mg) in formic acid (10mL of a 4.4% solution in methanol). Stir for several hours under a nitrogen atmosphere, filter and wash with methanol (10mL) followed by water (10mL). Combine the filtrate plus the methanol and water washes. Evaporate the solvent *in vacuo* to give the title compound.

Scheme A, Step f: 4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]amino]-alpha-methyl-benzenepropanoic acid, methyl ester

Dissolve methyl [2-methyl-3-(4-amino)phenyl)propionate (13.6g, 70.5mmol) in acetone (500mL) and treat with potassium carbonate (10.7g, 77.6mmol), potassium iodide (1.17g, 7.05mmol) and t-butyl bromoacetate (15.1g, 77.6mmol). Reflux for several hours, cool, filter and evaporate the solvent *in vacuo*. Purify by flash chromatography to give the title compound.

Scheme A, Step g: 4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]amino]-alpha-methyl-benzenepropanoic acid

Dissolve 4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]amino]-alpha-methyl-benzenepropanoic acid, methyl ester (9.95g, 32.4mmol) in anhydrous hexamethylphosporamide (160mL) and treat with sodium cyanide (1.59g, 32.4mmol). Heat at 70°C for 48 hours, cool and dilute with saturated ammonium chloride (300mL). Extract with ethyl ether (400mL), wash with water (2X300mL), then brine (300mL) and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by flash chromatography to give the title compound.

Scheme A, Step h: 2-[[4-[3-[(6-Amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]amino]-acetic acid, 1,1-dimethylethyl ester

Dissolve 4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]amino]-alpha-methyl-benzenepropanoic acid (1.07g, 3.64mmol) in tetrahydrofuran (15mL) and treat with N-methylmorpholine (0.4mL, 3.64mmol). Cool to -20°C and treat with isobutyl chloroformate (0.47mL, 3.64mmol). Stir for 30 minutes and add a solution of 1,3-dipropyl-5,6-diaminouracil (0.82g, 3.64mmol) in dimethylformamide (5mL). Stir for 3 hours at - 20°C, warm to room temperature and dilute with ethyl ether (200mL). Separate the organic phase, wash with water (200mL) and dry (MgSO4). Evaporate the solvent in vacuo and purify by flash chromatography to yield the title compound.

Scheme A, Step i: 2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylamino]acetic acid

Dissolve 2-[[4-[3-[(6-amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]amino]-acetic acid, 1,1-dimethylethyl ester (1.59g, 3.18mmol) in a mixture of ethanol (30mL) and 15% potassium hydroxide (30mL). Beat at 55°C and stir for 5 hours. Cool, acidify and dilute

Suspend lithium hydride (1.01g, 126.4mmol) in hexamethylphosphoramide (50mL) and treat with 1-propanethiol (11.5mL, 126.4mmol). Stir for 1.5 hours and add to a solution of 4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy-alpha-ethyl-benzeneacetic acid, methyl ester (5.57g, 18.06mmol) in hexamethylphosphoramide (50mL) under a nitrogen atmosphere. Stir for 20 hours and pour into ice cold 5% hydrochloric acid (500mL). Extract into ethyl ether (4X300mL), wash with water (500mL) and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by flash chromatography (5⇒10⇒20% isopropanol/hexane) to give the title compound (4.01g).

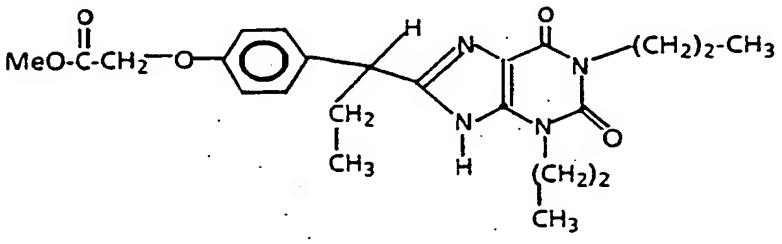
Scheme A, Step h: 2-[[4-[2-[(6-Amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-1-ethyl-3-oxoethyl]phenyl]oxy]-acetic acid, 1,1-dimethylethyl ester

Dissolve 4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy-alpha-ethyl-benzeneacetic acid (4.0g, 13.59mmol) in tetrahydrofuran (100mL) and treat with N-methylmorpholine (1.6mL, 13.59mmol). Cool to -20 °C and treat with isobutyl chloroformate (1.8mL, 13.59mmol). Stir for 45 minutes and add a solution of 1,3-dipropyl-5,6-diaminouracil (3.1g, 13.59mmol) in dimethylformamide (8mL). Stir for 3 hours at -20 °C, warm to room temperature and dilute with chloroform (400mL). Separate the organic phase, wash with saturated sodium hydrogen carbonate (200mL), then brine (300mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by flash chromatography (5⇒10 methanol/chloroform) to give the title compound (5.58g).

Scheme A, Step i: 2-[4-[1-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]aceticacid

Dissolve 2-[[4-[2-[(6-amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-1-ethyl-3-oxoethyl]phenyl]amino]-acetic acid, 1,1-dimethylethyl ester (5.57g, 11mmol) in ethanol (60mL) and treat with 15% potassium hydroxide (60mL). Heat at 55 °C for 6 hours, cool to 0 °C and acidify with concentrated hydrochloric acid (15mL) and water (200mL). Extract with chloroform (3X200mL), dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by flash chromatography (5⇒10⇒20% isopropanol/hexane) to give 2.5g crude product. Triturate with 10% isopropanol/hexane and dry to give the title compound (369mg); mp 220-25 °C (dec).

Example 8

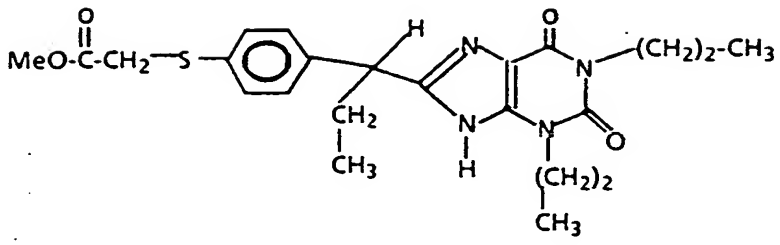


Preparation of 2-[4-[1-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid, methyl ester

Dissolve 2-[4-[1-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid (85.6g, 0.2mol) in methanol (500mL) and treat with concentrated sulfuric acid (0.5mL). Heat to 60 °C for 16 hours, cool and reduce the solvent by 50% *in vacuo*. Dilute with ethyl ether (500mL), wash with saturated sodium hydrogen carbonate, then brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound.

Example 9

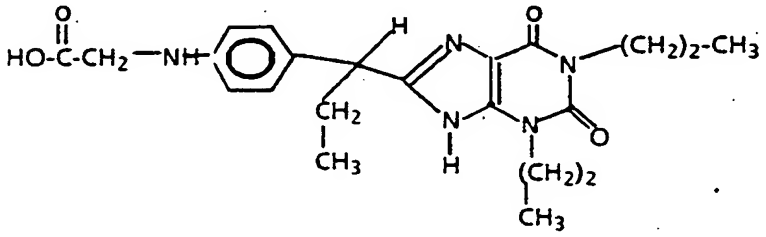
Example 10



Preparation of 2-[4-[1-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylthio]aceticacid, methyl ester

Dissolve 2-[4-[1-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylthio]acetic acid (88.8g, 0.2mol) in methanol (500mL) and treat with concentrated sulfuric acid (0.5mL). Heat to 60°C for 16 hours, cool and reduce the solvent by 50% *in vacuo*. Dilute with ethyl ether (500mL), wash with saturated sodium hydrogen carbonate, then brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound.

Example 11



Preparation of 2-[4-[1-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylamino]acetic acid

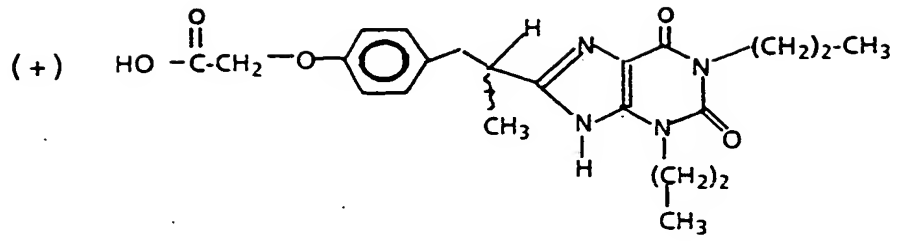
Scheme B, Step a: Methyl 4-(t-butylacetylamino)-phenylacetate

Dissolve methyl (4-aminophenyl)acetate (14.9g, 90.3mmol) in acetone (300mL). Add potassium carbonate (13.7g, 99.3mmol), potassium iodide (1.47g, 9.03mmol) and t-butyl bromoacetate (16mL, 99.3mmol). Heat at reflux for 20 hours then remove 200mL of acetone *in vacuo*. Dilute the residue with ethyl ether (500mL), wash with water (2X300mL) and brine (300mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by flash chromatography to give the title compound.

Scheme B, Step b: 4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]amino-alpha-ethyl-benzeneacetic acid, methyl ester

Mix lithium diisopropylamide (51mmol) and hexamethylphosphoramide (16.5g, 92mmol), cool to -78°C and place under a nitrogen atmosphere. Add a solution of methyl 4-(t-butylacetylamino)phenylacetate (6.42g, 23mmol) in tetrahydrofuran (50mL) and stir for 30 minutes. Add ethyl bromide (5g, 46mmol) and stir at -78°C for 4 hours. Add saturated ammonium chloride (200mL) and warm to room temperature. Add water (100mL), separate the organic phase and extract the aqueous phase with ethyl ether (3X200mL). Dry ($Na_2SO_4$) and evaporate the solvent *in vacuo*. Purify by flash chromatography to give the title compound.

Scheme A, Step g: 4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]amino-alpha-ethyl-benzeneacetic acid



Preparation of (+)-2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylamino]-acetic acid

Scheme A, step g: (+)-4-[[2-(1,1-Dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid

Dissolve 4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid, methyl ester (15.0g, 48.6mmol) in ethyl ether (50mL) and adsorb onto silica gel (45g). Evaporate the solvent under a stream of nitrogen and add pH 7 phosphate buffer (1500mL of a 0.1M solution) followed by lipase P-30 (15g). Maintain a ph of 7 by the addition of 1M sodium hydroxide. Stir for 24 hours, filter through silica gel and rinse the filter cake with chloroform (500mL). Separate the aqueous phase and extract with chloroform (4X300mL). Dry ($MgSO_4$) the combined organic phases and evaporate the solvent *in vacuo*. Purify by flash chromatography (10% methanol/chloroform) to give (-)-4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid, methyl ester (6.43g, 91% ee) and (+)-4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid (6.59g, 90% ee after reesterification with diazomethane).

Dissolve (+)-4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid (90% ee) (6.04g, 20.5mmol) in ethyl ether (400mL) and treat with excess diazomethane. Wash with saturated sodium hydrogen carbonate (2X300mL) and brine (300mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give (+)-4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid, methyl ester (5.85g).

Dissolve (+)-4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid, methyl ester (5.74g, 18.6mmol) in ethyl ether and adsorb onto silica gel (18g). Evaporate the solvent *in vacuo* to leave a white powder.

Suspend the powder in pH 7 phosphate buffer (600mL of a 0.1M solution). Add lipase P-30 (5.74g) and stir for 16 hours. Filter and extract with ethyl ether (3X400mL). Dry ($MgSO_4$), evaporate the solvent *in vacuo* and purify by flash chromatography (5⇒10% methanol/chloroform) to give the title compound (5.09g, 98% ee after reesterification with diazomethane); $[\alpha]_d^{20}$ = + 18.9° (C = 0.97; $CHCl_3$).

Scheme A, step h: (+)-2-[[4-[3-[(6-Amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)-amino]-2-methyl-3-oxopropyl]phenyl]oxy]-acetic acid, 1,1-dimethylethyl ester

Dissolve (+)-4-[[2-(1,1-dimethylethoxy)-2-oxoethyl]oxy]-alpha-methyl-benzenepropanoic acid (3.02g, 10.27mmol) in tetrahydrofuran (100mL) and treat with N-methylmorpholine (1.2mL, 10.27mmol). Cool to -20° C, add isobutyl chloroformate (1.35mL, 10.27mmol) and stir for 1 hour. Add a solution of 1,3-dipropyl-5,6-diaminouracil (2.33g, 10.27mmol) in dimethylformamide (8mL) and stir for 6 hours at -20° C. Warm to room temperature and dilute with chloroform (600mL). Wash with saturated sodium hydrogen carbonate (300mL), then brine (3X300mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by flash chromatography (5⇒10⇒15⇒20% isopropanyl/hexane) to give the title compound as a foam (3.74g, 72%); $[\alpha]_d^{20}$ = + 51.4° (C = 1.03, $CHCl_3$).

Scheme A, step i: (+)-2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid

Dissolve (+)-2-[[4-[3-[(6-amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]oxy]-acetic acid, 1,1-dimethylethyl ester (2.20g, 4.38mmol) in benzene (100mL) and treat with triethyloxonium tetrafluoroborate (35mL of a 1M solution in methylene chloride, 35.02mmol) and place under a nitrogen atmosphere. Heat at 40° C for 24 hours, cool and dilute with phosphate buffer (400mL). Extract into ethyl ether (3X300mL), dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by

isopropanol/hexane) to give the title compound (2.16g, 66%); $[\alpha]_d^{20}$ = - 45.8° (C = 1.00, $CBCl_3$).

Scheme A, step i: (-)-2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid

Dissolve (-)-2-[[4-[3-[(6-amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]oxy]-acetic acid, 1,1-dimethylethyl ester (1.76g, 3.50mmol) in benzene (500mL) and treat with triethyloxonium tetrefluoroborate (28mL of a 1M solution in methylene chloride, 28mmol) and heat at 50°C for 20 hours. Cool, dilute with ethyl ether (300mL) and wash with phosphate buffer (500mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by radial chromatography (2⇒4% methanol/chloroform) to give the ethyl enolate of (-)-2-[[4-[3-[(6-amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]oxy]-acetic acid, 1,1-dimethylethyl ester (1.14mg, 61%); $[\alpha]_d^{20}$ = - 64.1° (C = 1.16, $CHCl_3$).

Dissolve the ethyl enolate of (-)-2-[[4-[3-[(6-amino-1-propyl-1,2,3,4-tetrahydro-3-propyl-2,4-dioxo-5-pyrimidinyl)amino]-2-methyl-3-oxopropyl]phenyl]oxy]-acetic acid, 1,1-dimethylethyl ester (1.01g, 1.9mmol) in anhydrous benzene (200mL) and heat at 80°C for 24 hours. Evaporate the solvent *in vacuo* and purify the residue by radial chromatography (40⇒50% ethyl acetate/hexane) to give (-)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid, ethyl ester (0.7g, 81%); $[\alpha]_d^{20}$ = - 54.3° (C = 0.856, $CBCl_3$).

Dissolve (-)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid, ethyl ester (0.62g, 1.36mmol) in ethanol (15mL) and treat with a solution of potassium hydroxide (0.091g, 1.63mmol) in water (15mL). Stir for 3 hours, add water (200mL) and wash with ethyl ether (300mL). Acidify the aqueous phase with 10% hydrochloric acid and extract into chloroform (4X150mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound (0.47g, 81%); $[\alpha]_d^{20}$ = - 79.1° (C = 0.537, DMSO).

The following compounds can be prepared by procedures analogous to those described in Examples 1-14:

2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]propionic acid ;

2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylthio]propionic acid ;

2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylamino]propionic acid .

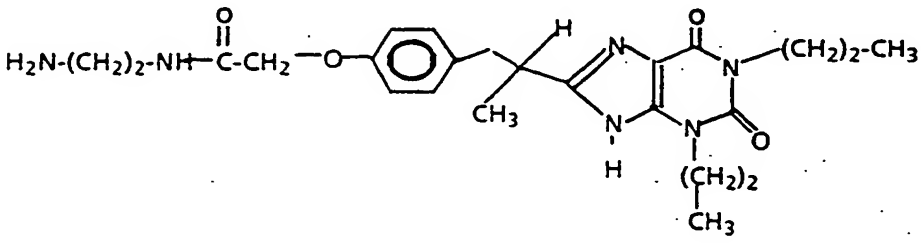
The compounds of formula (II) can be prepared by techniques and procedures well known and appreciated by one of ordinary skill in the art. A general synthetic procedure for the preparation of compounds of formula (II) is set forth in Scheme C. In Scheme C, all substituents, unless otherwise indicated, are as previously defined.

aminoethyl)alkanamide peptide of structure (19) is then deprotected to give the [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]phenylhetero-N-(2-aminoethyl)alkanamide peptide of structure (19).

The selection, utilization and subsequent deprotection of suitable amino acid and peptide amino protecting groups are well known to one of ordinary skill in the art and are described in "Peptide Synthesis' Miklos Bodanszky, Wiley (1966).

The following examples present typical syntheses as described in Scheme C. These examples are illustrative only and are not intended to limit the scope of the present invention in any way.

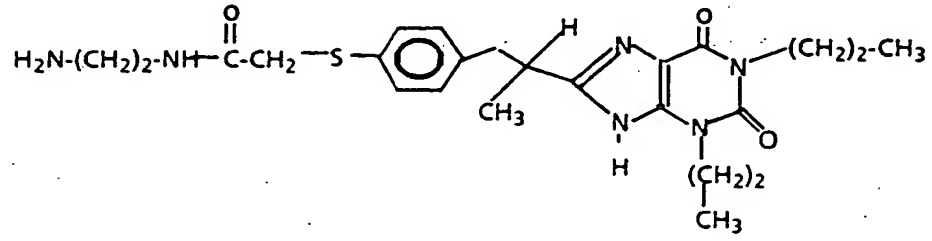
Example 15



Preparation of N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]-phenoxy]-acetamide

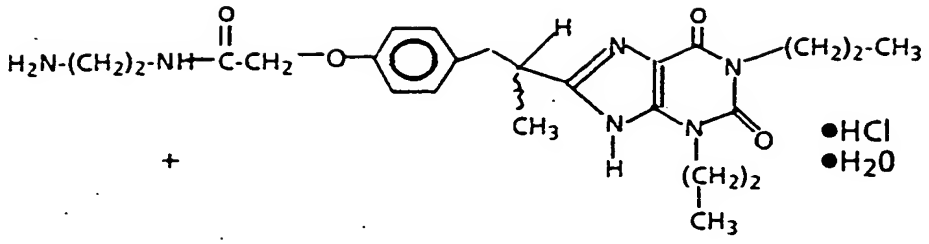
Dissolve 2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid (800mg, 1.87mmol) in dimethylformamide (20mL) and treat with N-hydroxysuccinimide (215mg, 1.87mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (751mg, 3.92mmol). Stir for 1 hour and add to a stirring solution of ethylenediamine (20mL of a 10% solution in methanol). Stir for 1 hour and dilute with chloroform (600mL). Separate the organic phase, wash with 5% sodium carbonate (200mL), then brine (300mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by radial chromatography (5⇒10% methanol/chloroform with 1% ammonium hydroxide) and recrystallize (10% isopropanol/hexane) to give the title compound (364mg); mp 143-44 °C.

Example 16



Preparation of N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]-phenylthio]-acetamide

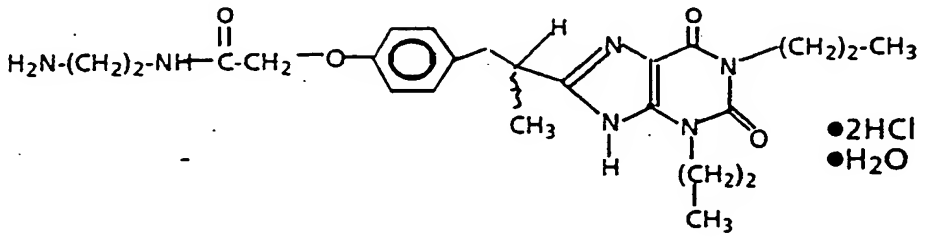
Dissolve 2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenylthio]acetic acid (785mg, 1.87mmol) in dimethylformamide (20mL) and treat with N-hydroxysuccinimide (215mg, 1.87mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (751mg, 3.92mmol). Stir for 1 hour and add to a stirring solution of ethylenediamine (20mL of a 10% solution in methanol). Stir for 1 hour and dilute with chloroform (600mL). Separate the organic phase, wash with 5% sodium carbonate (200mL), then brine (300mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by radial chromatography to give the title compound.



Preparation of (+)-N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro -1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]-phenoxy]-acetamide

Dissolve (+)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid (0.28g, 0.65mmol) in dimethylformamide (10mL) and treat with N-hydroxysuccinimide (0.074g, 0.65mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.262g, 1.37mmol). Stir for 1 hour and add a solution of ethylenediamine (10mL of a 10% solution in methanol) and stir for 1 hour. Dilute with chloroform (500mL), wash with 5% sodium carbonate (200mL) and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by radial chromatography (10⇒20% methanol/chloroform with 1% ammonium hydroxide). Dissolve the purified material in 5% methanol/ethyl ether and treat with ethereal hydrochloric acid. Evaporate the solvent in vacuo and triturate the residue with ethyl ether. Filter the resulting solid and dry to give the title compound (88mg); $[\alpha]_d^{20}$ = + 75.7° (C = 0.96, $H_2O$).
Anal. Calcd for $C_{24}H_{34}N_6O_4 \cdot HCl \cdot H_2O$: C, 54.90; H, 7.10; N, 16.01;
Found: C, 55.31; H, 7.47; N, 15.76.

Example 20

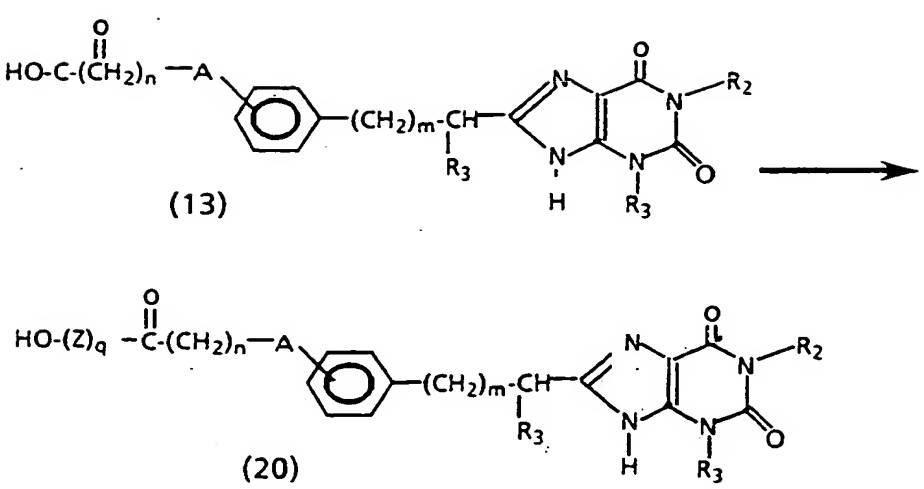


Preparation of (-)-N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro -1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]-phenoxy]-acetamide

Dissolve (-)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid (0.45g, 1.05mmol) in dimethylformamide (20mL) and treat with N-hydroxysuccinimide (0.12g, 1.05mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.42g, 2.20mmol). Stir for 85 minutes and add to a solution of ethylenediamine (10% in methanol). Stir for 26 hours and dilute with chloroform (500mL). Separate the organic phase and wash with 5% sodium carbonate, then brine (400mL). Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by radial chromatography (10⇒20% methanol/chloroform with 1% ammonium hydroxide) to give an oil (370mg). Dissolve the oil in ethyl ether, treat with ethereal hydrochloric acid and evaporate the solvent *in vacuo*. Triturate the residue with ethyl ether, filter and dry to give the title compound (361mg); $[\alpha]_d^{20}$ = - 80.8° (C = 0.95, $H_2O$).
Anal. Calcd for $C_{24}H_{34}N_6O_4 \cdot 2HCl \cdot H_2O$: C, 51.34; H, 6.82; N, 14.97;
Found: C, 51.74; H, 6.69; N, 14.83.

Example 21

Scheme D



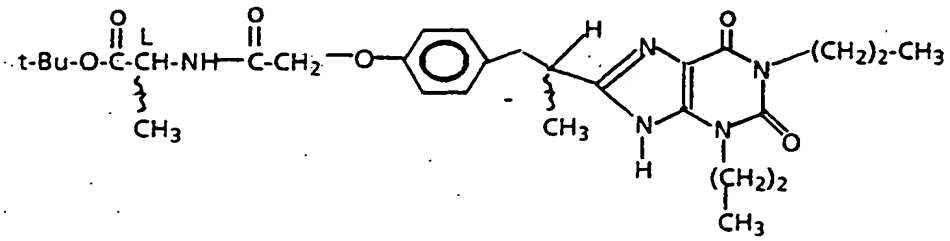
Scheme D provides a general synthetic procedure for the preparation of compounds of formula (III).

An appropriate [[2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]phenylhetero alkanoic acid of structure (13) is amidated with a suitable carboxylate protected amino acid or peptide to give the [[2,3,6,9-tetrahydro -1,3-dialkyl-2,6-dioxo-1H-purin-8-yl]alkyl]phenylhetero alkanamide peptide of structure (20) after deprotection as described previously in Scheme C.

Starting materials for use in the general synthetic procedure outlined in Scheme D are readily available to one of ordinary skill in the art.

The following examples present typical syntheses as described by Scheme D. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way.

Example 22



Preparation of (-)-N-[[[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propy]phenyl]oxy]acetyl]-L-alanine, t-butyl ester

Mix (-)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid (4.28g, 10mmol), L-alanine t-butylester hydrochloride (965mg, 5.3mmol), hydroxybenztriazole (1.65g, 11mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.1g, 11mmol). Add a solution of diisopropylethylamine (3.8mL) in methylene chloride (20mL) and stir at room temperature for several hours. Dilute with ethyl acetate (150mL), wash with cold 0.5N hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound.

Example 23

and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

A therapeutically effective $A_1$-antagonistic amount of a compound of formula (I), (II) or (III) will generally vary from about 0.5 milligram per kilogram of body weight per day (mg/kg/day) to about 500 mg/kg/day. A daily dose of from about 5 mg/kg to about 50 mg/kg is preferred.

In effecting treatment of a patient, pharmaceutical compositions containing the compounds of formula (I), (II) or (III) can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, they can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

Compounds of formula (I), (II) or (III) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining the compounds of formula (I), (II) or (III) with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

In another embodiment, the present invention provides compositions comprising a compound of formula (I), (II) or (III) in admixture or otherwise in association with one or more inert carriers. These compositions are useful, for example, as assay standards, as convenient means of making bulk shipments, or as pharmaceutical compositions. An assayable amount of a compound of formula (I), (II) or (III) is an amount which is readily measurable by standard assay procedures and techniques as are well known and appreciated by those skilled in the art. Assayable amounts of a compound of formula (I), (II) or (III) will generally vary from about 0.001% to about 75% of the composition by weight. Inert carriers can be any material which does not degrade or otherwise covalently react with a compound of formula (I), (II) or (III). Examples of suitable inert carriers are water; aqueous buffers, such as those which are generally useful in High Performance Liquid Chromatography (HPLC) analysis; organic solvents, such as acetonitrile, ethyl acetate, hexane and the like; and pharmaceutically acceptable carriers or excipients.

More particularly, the present invention provides pharmaceutical compositions comprising an effective amount of a compound of formula (I), (II) or (III) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solution, suspensions, or the like.

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds of formula (1) may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of formula (1), the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the active ingredient present in compositions is such that a unit dosage form suitable for administration will be obtained.

The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants, such as magnesium stearate or Sterotex; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin may be added or flavoring agents, such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration, the compounds of formula (I), (II) or (III) may be

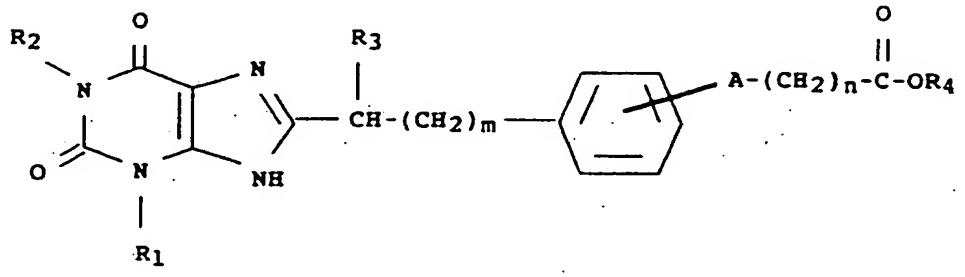
Table 1

| $A_1$- and $A_2$-Adenosine Receptor Affinity Activity of 8-Substituted Purines | | |
|---|---|---|
| Compound | $IC_{50}$ Adenosine $A_1$ (nM) | $IC_{50}$ Adenosine $A_2$ (nM) |
| 101673 | 1183 | >10,000 |
| 101699 | 327 | 5700 |
| 101345 | 14 | 36 |
| 102130 | 4.4 | 60 |
| 101993 | 60 | 1800 |
| 100991 | 10 | 300 |

101673 = 2-[4-[1-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetic acid
101699 = 2-[4-[2-(2,3,6,9-Tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8- yl)propyl]phenoxy]acetic acid
101345 = N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide
102130 = N-(2-Aminoethyl)-2-[4-[1-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide
101993 = (+)-N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide
100991 = (-)-N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide

## Claims

1. A compound of the formula I

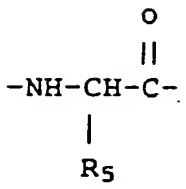


(I)

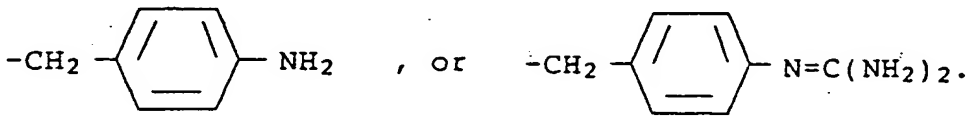
wherein
$R_1$, $R_2$ and $R_3$ are each independently a $C_1$-$C_4$ alkyl,
m is an integer 0, 1 or 2,
A is O, S, or NH,
n is an integer 1, 2 or 3, and
$R_4$ is H or a $C_1$-$C_4$ alkyl.

2. A compound of the formula II

A is O, S, or NH,
n is an integer 1, 2 or 3,
Z is a radical of the formula



q is an integer 1, 2 or 3, and
$R_5$ is a radical selected each time taken from the group consisting of H, $CH_3$, $-CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2N=C(NH_2)_2$, $-CH_2CH_2CH_2CH_2N=C(NH_2)_2$,



4. A pharmaceutical composition comprising a compound of Claim 1, 2 or 3.

5. A pharmaceutical composition according to claim 4 useful in the treatment for Alzheimer's Disease.

6. A pharmaceutical composition according to Claim 4 useful in the treatment for congestive heart failure.

7. A pharmaceutical composition according to Claim 4 useful in the treatment for pulmonary bronchoconstriction.

8. A composition comprising an assayable amount of a compound of Claim 1, 2 or 3 in admixture or otherwise in association with an inert carrier.

9. A pharmaceutical composition comprising an effective immunosuppressive amount of a compound of Claim 1, 2 or 3 in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

10. A compound according Claim 2 wherein the compound is N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide.

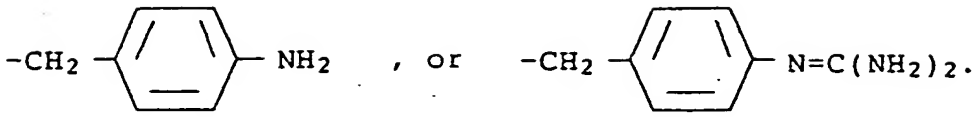
11. A compound according Claim 2 wherein the compound is N-(2-Aminoethyl)-2-[4-[1-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide.

12. A compound according Claim 10 wherein the compound is (+)-N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide.

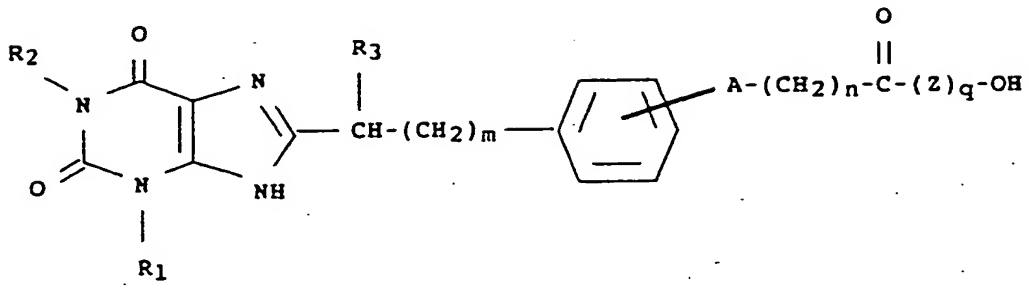
13. A compound according Claim 10 wherein the compound is (-)-N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide.

**Claims for the following Contracting State: GR**

1. A compound of the formula I



3. A compound of the formula III



(III)

wherein

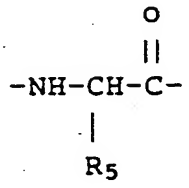
$R_1$, $R_2$ and $R_3$ are each independently a $C_1$-$C_4$ alkyl,

m is an integer 0, 1 or 2,

A is O, S, or NH,

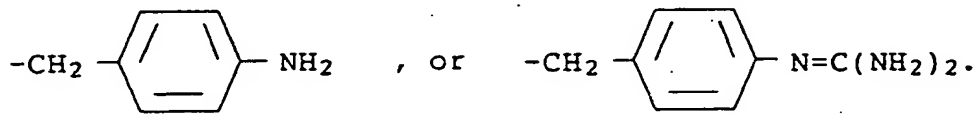
n is an integer 1, 2 or 3,

Z is a radical of the formula



q is an integer 1, 2 or 3, and

$R_5$ is a radical selected each time taken from the group consisting of H, $CH_3$, $-CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2N=C(NH_2)_2$, $-CH_2CH_2CH_2CH_2N=C(NH_2)_2$,

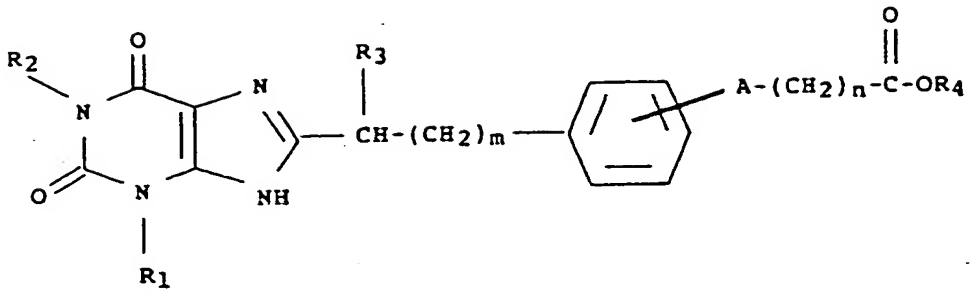


4. A method of preparing a pharmaceutical composition comprising combining a compound of claim 1, 2 or 3 with a pharmaceutically acceptable carrier.

5. A method according to Claim 4 wherein the pharmaceutical composition prepared is useful in the treatment for Alzheimer's Disease.

6. A method according to Claim 4 wherein the pharmaceutical composition prepared is useful in the treatment for congestive heart failure.

7. A method according to Claim 4 wherein the pharmaceutical composition prepared is useful in the

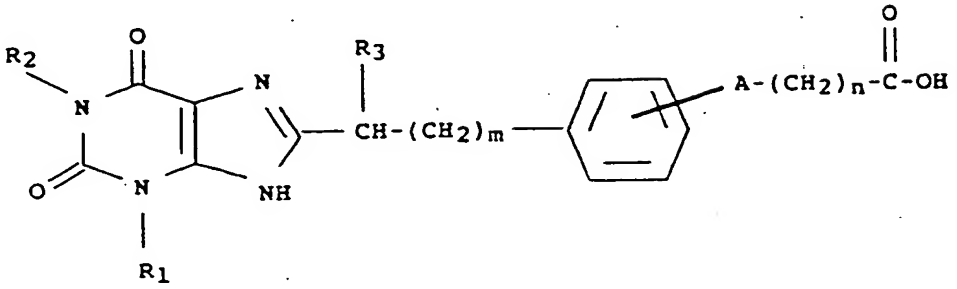


(Ib)

wherein

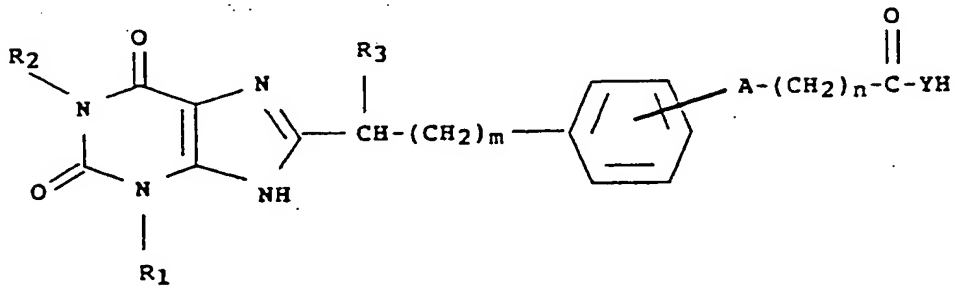
$R_1$, $R_2$ and $R_3$ are each independently a $C_1$-$C_4$ alkyl,
m is an integer 0, 1 or 2,
A is O, S, or NH,
n is an integer 1, 2 or 3, and
$R_4$ is a $C_1$-$C_4$ alkyl

comprising esterifying a compound of formula



in which all the substituents are defined as above.

3. A process for preparing compounds of the formula IIa



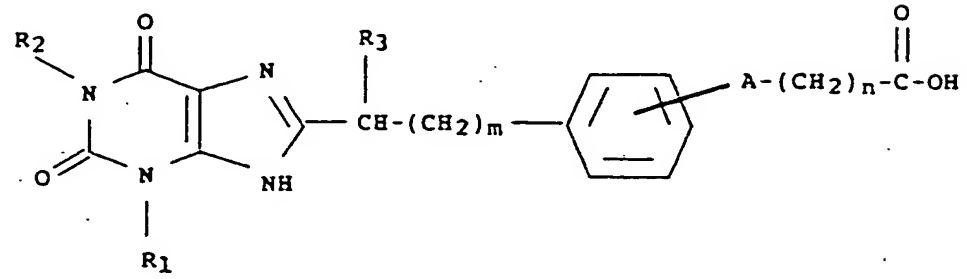
(IIa)

wherein

$R_1$, $R_2$ and $R_3$ are each independently a $C_1$-$C_4$ alkyl,
m is an integer 0, 1 or 2,
A is O, S, or NH,
n is an integer 1, 2 or 3,
Y is $-NH(CH_2)_pNH-$ and
p is an integer 2, 3 or 4,

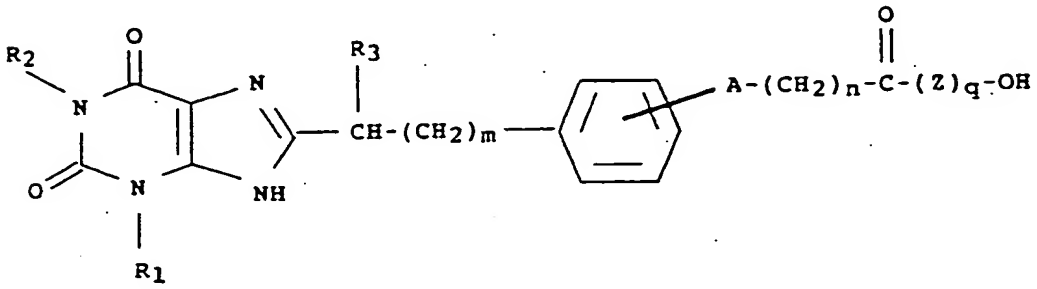
comprising amidating a compound of formula

comprising amidation and subsequent deprotection of a compound of the formula,



in which all the substituents are defined as above, with the appropriate protected amino acid or peptide.

5. A process for preparing compounds of the formula III



(III)

wherein

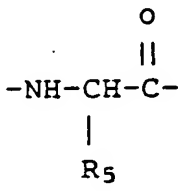
$R_1$, $R_2$ and $R_3$ are each independently a $C_1$-$C_4$ alkyl,

m is an integer 0, 1 or 2,

A is O, S, or NH,

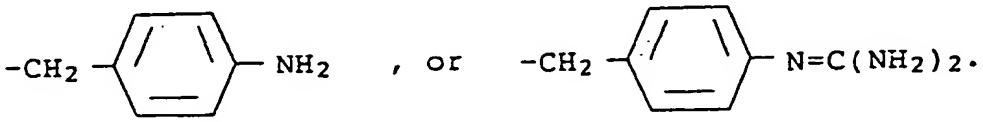
n is an integer 1, 2 or 3,

Z is a radical of the formula



q is an integer 1, 2 or 3, and

$R_5$ is a radical selected each time taken from the group consisting of H, $CH_3$, $-CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2N=C(NH_2)_2$, $-CH_2CH_2CH_2CH_2N=C(NH_2)_2$,



comprising amidation and subsequent deprotection of a compound of formula,